Ethical Guidelines in Clinical Research

DR.RLC.SASIDHAR
Associate Professor, CHIPS

Physician/Patient Relationship

- Dilemmas of physicians and health care providers with conflicting roles of helping the patient and gaining scientific knowledge.

- A properly designed and conducted clinical trial is an ethically appropriate way to acquire new knowledge.

- Clinical decisions for patient treatment without strong evidence of rigorous scientific support has ethical questions.

Clinical Research or Clinical Practice???

- How often is a physician certain of the outcome from a specific therapy for a particular patient?
  - If patient's reaction is predictable, applying treatment is practice.
  - Physician is unsure of the outcome, applying the treatment could be considered research.

- Actions by the physician for the benefit of individual patients have the potential of increasing scientific knowledge.

- Scientific knowledge gained from research can be of benefit to individual patients.

When do ethical questions arise?

- Unproven therapies are proposed to replace proven ones and are particularly acute for chronic or fatal illness.

- Clinical trials are one of several settings in which the physician's duty extends beyond his/her responsibility to the individual patient.

- Example: vaccinations against communicable disease are promoted by physicians, yet the individual vaccinated incurs a small risk to benefit the population as whole.

Randomization (1)

- Physicians and patients may feel it is inappropriate to base a patient's treatment on chance.
- Physicians may feel an obligation to have a preference even when the evidence does not favor any particular treatment.
- Randomization is justified when there is relative ignorance about the best treatment.

Randomization (2)

- Physicians and patients with firm preferences for treating a particular indication should not participate in a clinical trial.
- Patients with strong preference about a treatment are likely to become easily dissatisfied with randomization to a treatment in the clinical trial.
- Physicians with strong convictions could bias the clinical trial in a different direction.

Informed Consent

- Patients (or parents/guardians/family members) must sign an informed consent prior to participation in a research study.
- Sick and dying patients and their families maybe vulnerable and technical information may be presented in complicated ways!!!
- Informed consent procedures were developed to protect patients from exploitation.
- Currently informed consent is viewed as protection from litigation.
- IRB must evaluate the informed consent form prior to the start of the study.

Confidentiality

- The U.S. Department of Health and Human Service (HHS) sets the Standards for Privacy of Individually Identifiable Health Information under the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

- This provided the first comprehensive Federal protection for the privacy of personal health information.

- Took effect April 14, 2003.

- The DHHS (web site http://privacyruleandresearch.nih.gov) for further information about HIPAA.

Oversight Groups

- Institutional Review Boards
  - Checklist for informed consent
  - Informed consent sample information
- Scientific Review Committees
- Data and Safety Monitoring Boards
  - NCI policy on DSMBs
- Office for Protection from Research Risks (OPRR)

Other Committees

Steering committee

Executive committee

Treatment effects monitoring committee (DSMB)

Advisory review committee (Conduct)

.

.

.

Active-control Trials

- Placebo trials are not always ethical.
- Placebo control is untenable when the disease is life-threatening and an effective therapy is available.
- Comparison is made between active control and the experimental treatment or therapy.

Historical Perspective

- Nuremberg trials (1946-47): atrocities in WWII concentration camps committed by Nazi physicians.
- 20 of the 23 tried for the crimes were physicians.
- No international standards for ethical conduct in human experimentation during this time.
- Results: Nuremberg Code adopted in 1947.

Nuremberg Code

- Voluntary consent is essential
- Must be no reasonable alternative to conducting the experiment
- Anticipated results must have a basis in biological knowledge and animal experimentation must have potential for meaningful results for the good of society.
- Avoid unnecessary physical and mental suffering and injury.
- No expectation of death or disability.
- Risk should not exceed humanitarian importance.
- Protection against even a remote possibility of death or injury.
- Qualified scientists.
- Subject can stop at will.
- Investigator has an obligation to terminate the experiment if injury or death seems likely.

Helsinki Declaration

- The World Medical Association (WMA) adopted a formal code of ethics for physicians engaged in clinical research in 1964 in Helsinki, Finland.

- Latest complete revision in 2000 (Helsinki Declaration).

- It reiterates the principles of Nuremberg Code with particular attention to the duty of physician to protect the life and health of human subjects.

- Written protocol must be reviewed by an ethical review committee independent from the investigator.

Other International Guidelines

1. International Covenant of Civil and Political Rights (1976) adopted by the United Nations General Assembly.

2. The World Health Organization (WHO)

3. The Council for International Organizations of Medical Sciences (CIOMS) issued the International Ethical Guidelines for Biomedical Research Involving Human Subjects.

Tuskegee Syphilis Experiment

- The U.S. government's 40-year experiment on black men with syphilis in Tuskegee, Alabama (1936).
- Long after the availability of penicillin, a proven cure in the 50's, the US Public Health Service studied untreated black men.
- The study was stopped in the early 1970's after it was publicized.
- President Clinton's apology for the Tuskegee Syphilis Experiment to the eight remaining survivors, May 16, 1997.

Modern Perspective

- Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research through the 1974 National Research Act.

- The Commission produced the Belmont Report in 1974 which distilled basic ethical guidelines in research with human subjects.

- Three principles: respect of persons or individual autonomy, beneficence and justice.

Individual Autonomy – patients have the right to decide what should be done for them with respect to their illness unless the result would be clearly detrimental to others.

Beneficence – patient's right to receive advantageous or favorable treatment.

Justice – fairly distributing the benefits and burdens of research.

IRB

- The U.S. National Institute of Health Policies for the Protection of Human Subjects (1966) established the IRB to protect human participants in research.

- In 1981, U.S. regulations required IRB approval for all drugs or products regulated by the FDA.

- Prerequisites set forth by the FDA:
  - Risks to participants are minimized
  - Risks are reasonable in relation to the anticipated benefits
  - Selection of study participants is equitable
  - Informed consent obtained appropriately
  - Adequate provisions for monitoring data collection
  - Privacy of the participants and the confidentiality of the data protected

Components of Informed Consent

- Research nature of the study
- Reasonable foreseeable risks and discomfort
- Potential benefits and alternatives
- Procedures for maintaining privacy
- Treatment for injuries incurred
- Individuals to contact for questions
- Voluntary nature of the study and the possibility of withdrawal at any time
- Not entering the study does not lead to loss of benefits